the final time. Three hours after dosing on day 8, animals are anesthetized by inhalation of isoflurane, and blood obtained is via cardiac puncture (0.5-0.7 ml). Whole blood is transferred to serum separator tubes, chilled on ice and permitted to clot. Serum is obtained after centrifugation at 4°C and frozen until analysis for compound levels. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

The animals dosed with vehicle have average triglycerides values of about 170 to 230 mg/dl, which are reduced by the positive PPARγ control (about 70 to 120 mg/dl with a mean reduction of 50%). Male db/db mice are hyperglycemic (average glucose of about 680 to 730 mg/dl on the 7th day of treatment), while lean animals have average glucose levels between about 190 and 230 mg/dl. Treatment with the positive control agent reduces glucose significantly (about 350 to 550 mg/dl with a mean decrease towards normalization of 56%).

Glucose is measured colorimetrically by using commercially purchased reagents (Sigma #315-500). According to the manufacturers, the procedures are modified from published work (McGowan et al. *Clin Chem*, 20:470-5 (1974) and Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129th Meeting ACS, 31C (1956).); and depend on the release of a mole of hydrogen peroxide for each mole of analyte coupled with a color reaction first described by Trinder (Trinder, P. *Ann Clin Biochem*, 6:24 (1969)). The absorbance of the dye produced is linearly related to the analyte in the sample. The assays are further modified for use in a 96 well format. Standards (Sigma #339-11, Sigma #16-11, and Sigma #CC0534 for glucose, triglycerides and total cholesterol, respectively), quality control plasma (Sigma # A2034), and samples (2 or 5 µl/well) are measured in duplicate using 200 µl of reagent. An additional aliquot of sample, pipetted to a third well and diluted in 200 µl water, provided a blank for each specimen. Plates are incubated at room temperature (18, 15, and 10 minutes for glucose, triglycerides and total cholesterol, respectively) on a plate shaker and absorbance read at 500 nm (glucose and total cholesterol) or 540 nm (triglycerides) on a plate reader. Sample absorbance is compared to a standard curve (100-800, 10-500, and 100-400 mg/dl for glucose, triglycerides and total cholesterol, respectively). Values for the quality control sample are consistently within the expected range and the coefficient

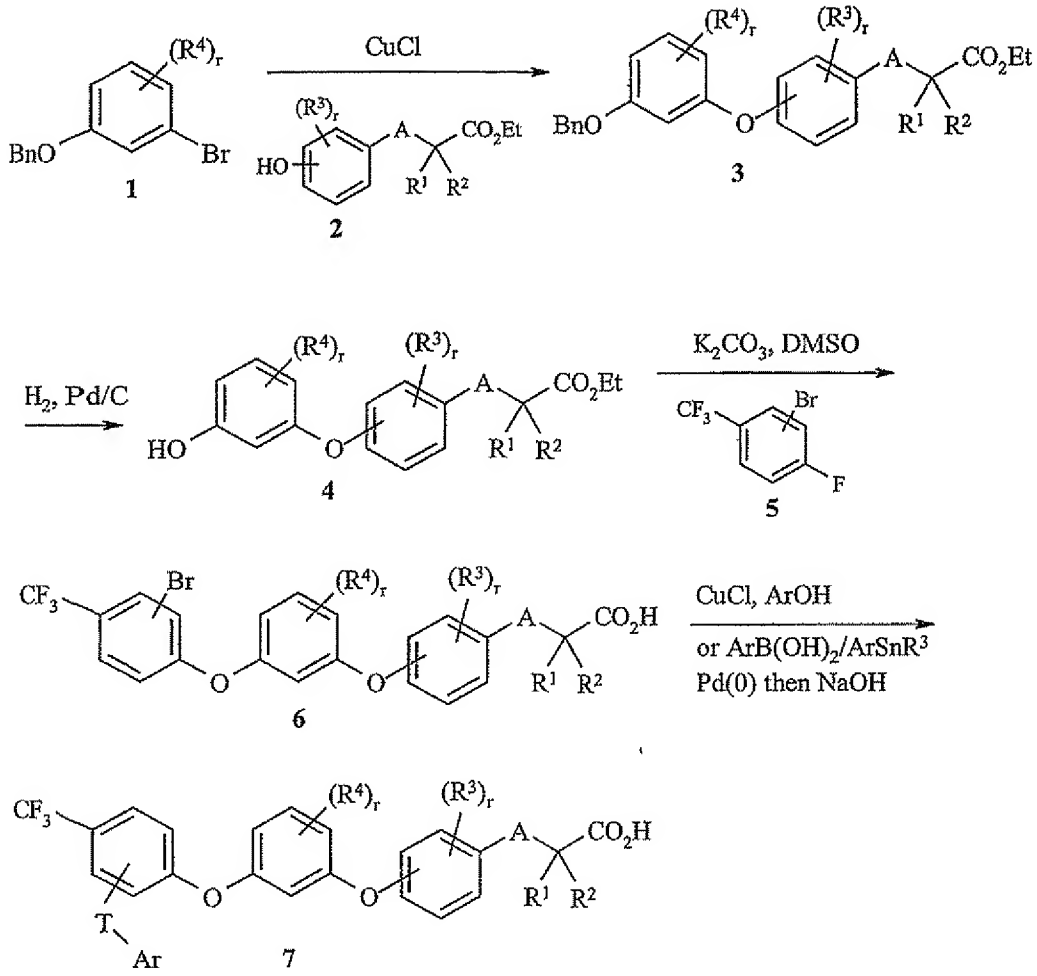
of variation for samples is below 10%. All samples from an experiment are assayed at the same time to minimize inter-assay variability.

Serum lipoproteins are separated and cholesterol is quantitated with an in-line detection system. Sample is applied to a Superose® 6 HR 10/30-size exclusion column (Amersham Pharmacia Biotech) and eluted with phosphate buffered saline-EDTA at 0.5 ml/min. Cholesterol reagent (Roche Diagnostics Chol/HP 704036) at 0.16 ml/min is mixed with the column effluent through a T-connection, and the mixture is passed through a 15 m x 0.5 mm id knitted tubing reactor immersed in a 37°C water bath. The colored product produced in the presence of cholesterol is monitored in the flow stream at 505 nm, and the analog voltage from the monitor is converted to a digital signal for collection and analysis. The change in voltage corresponding to change in cholesterol concentration is plotted against time, and the area under the curve corresponding to the elution of VLDL, LDL and HDL is calculated (Perkin Elmer Turbochrome software).

The compounds of the present invention can be prepared according to the procedures of the following schemes and examples, which may further illustrate details for the preparation of the compounds of the present invention. The compounds illustrated in the schemes and examples are, however, not to be construed as forming the only genus that is considered as the present invention.

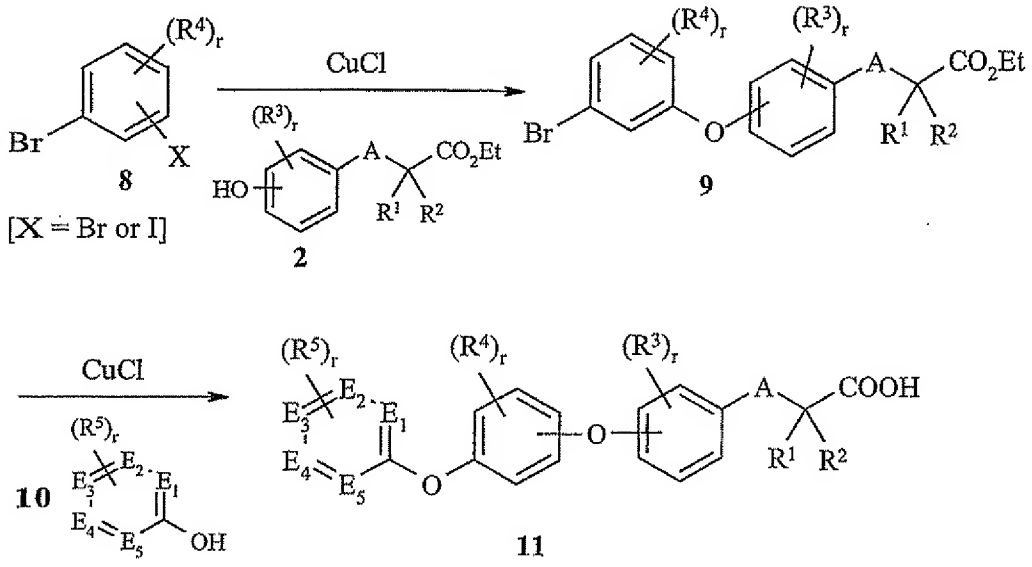
The compounds of the present invention, in general, may be prepared according to the Reaction Schemes 1-5 described below. It is understood that the reaction can be carried out under various coupling conditions as appropriate, such as Ullmann, Suzuki and Stille coupling conditions.

Reaction Scheme 1



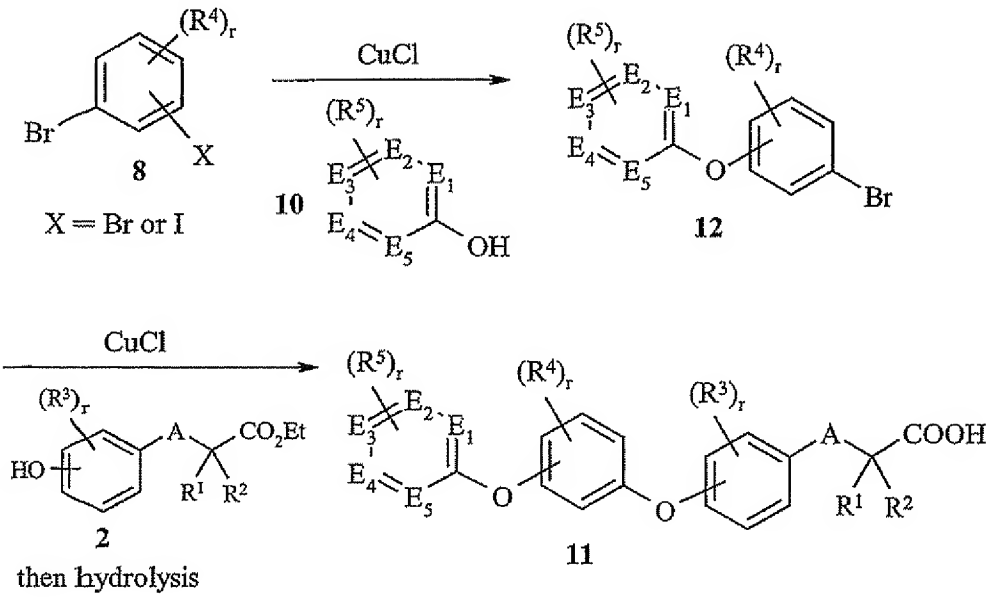
As shown in Reaction Scheme 1, aryl bromide **1** is treated with various phenols **2** under the Ullmann coupling condition to afford a coupled intermediate compound **3**. Benzyl group is removed from **3** under a catalytic hydrogenation condition to provide phenol **4**. The second phenoxy ether moiety is introduced by treating compound **4** with aryl fluoride **5** under a basic condition. Final substituent on the tail phenoxy ring (T-Ar) is installed under the Ullmann or Suzuki coupling condition, and a final acid compound **7** is obtained via a saponification.

Reaction Scheme 2



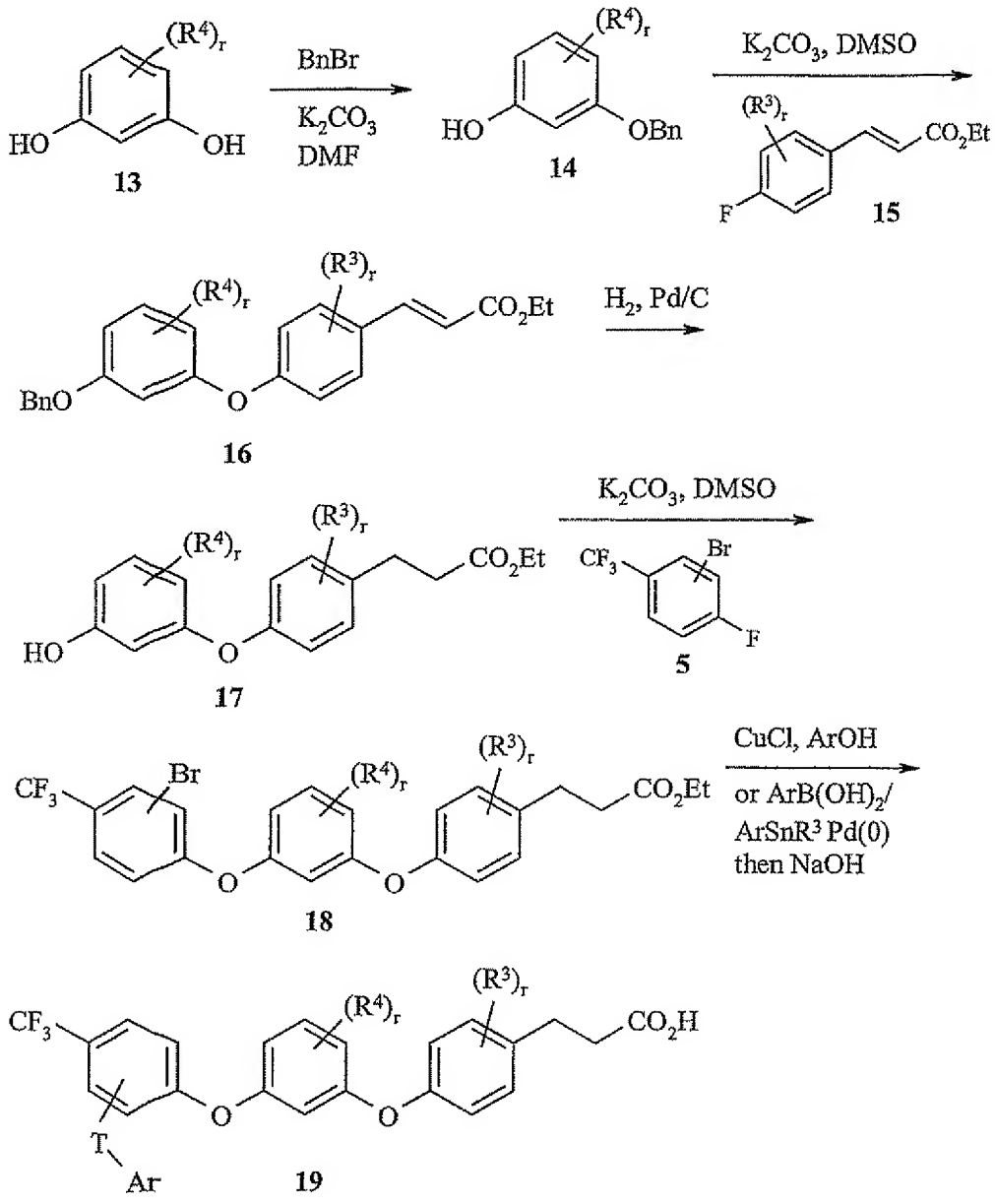
As shown in Reaction Scheme 2, aryl halide **8** is treated with various phenols **2** under the Ullmann coupling condition to afford a coupled intermediate compound **9**. The second phenoxy ether moiety is introduced by treating **9** with phenol **10** under the Ullmann condition and then a subsequent saponification affords the acid compound **11**.

Reaction Scheme 3



Alternatively, acid compound **11** can be prepared via a route shown in Reaction Scheme 3. Aryl halide **8** is treated with various phenols **10** under the Ullmann coupling condition to afford a coupled intermediate compound **12**. The second phenoxy ether moiety is introduced by treating **12** with phenol **2** under the Ullmann condition. Subsequent saponification affords the acid compound **11**.

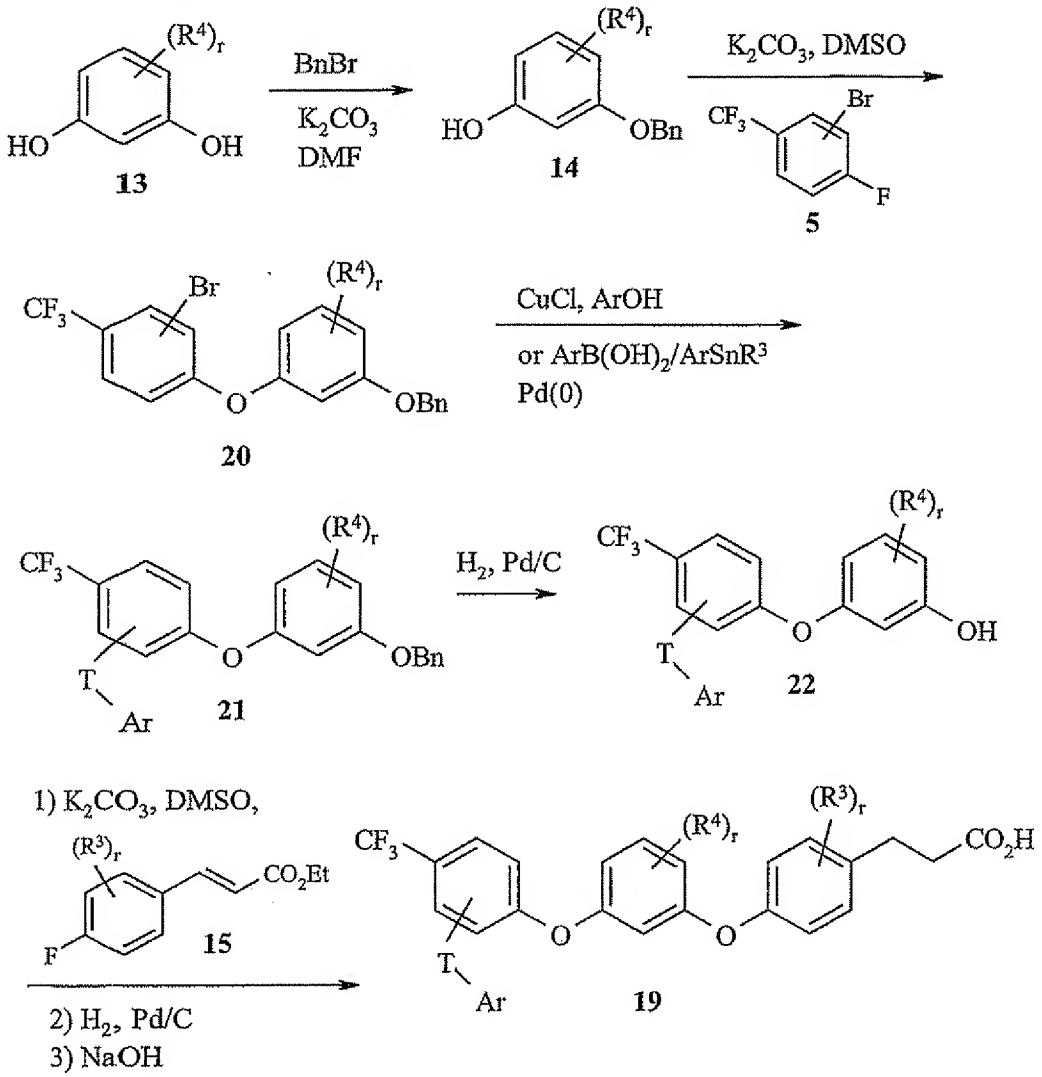
Reaction Scheme 4



As shown in Reaction Scheme 4, phenol **13** is monobenzylated to give compound **14**. The phenoxy ether moiety is introduced by treating **14** with aryl fluoride **15** under a basic condition. Removal of benzyl group under a catalytic hydrogenation condition and reduction of cinnamate double bond affords intermediate **17**, which is then treated with aryl fluoride **5** to provide compound **18**. Final substituent on the tail phenoxy

ring (T-Ar) is installed under the Ullmann or Suzuki coupling condition, and a subsequent saponification afford the acid compound **19**.

Reaction Scheme 5



Alternatively, compound **19** can be prepared via a route shown in Reaction Scheme 5. Phenol **13** is monobenzylated to give compound **14**, which is then treated with aryl fluoride **5** to give compound **20**. Under the Ullmann or Suzuki condition, the substituent on the tail phenyl ring (T-Ar) is installed to give compound **21**. Benzyl group is then removed under a catalytic hydrogenation condition to provide compound **22**. The second phenoxy moiety is introduced by treating compound **22** with aryl fluoride **15**

under a basic condition. The double bond in the cinnamate **15** is reduced via a catalytic hydrogenation, and a subsequent saponification affords the final acid compound **19**.

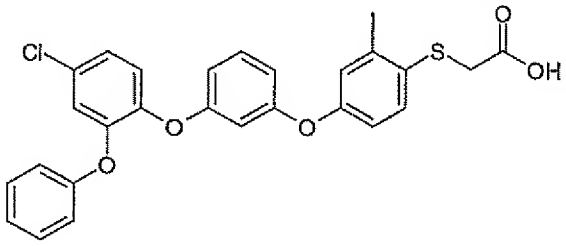
In the Schemes, Procedures and Examples below, various reagent symbols and abbreviations have the following meanings.

ACN	Acetonitrile
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropylethylamine
DMAP	4-dimethylamino pyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
eq (equiv)	equivalent(s)
ESI-MS	electron spray ion-mass spectroscopy
Et	ethyl
EtOAc	ethyl acetate
h	hours
HOAc	acetic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass
LRMS	low resolution mass
Me	methyl
Ms	methanesulfonyl
NBS	N-bromosuccinimide
Ph	phenyl
Pr	propyl
rt (r.t.)	room temperature
TBAI	tetrabutylammonium iodide
TBS	tertbutyldimethylsilyl
TFA	trifluoroacetic acid
TEA	triethylamine

THF	tetrahydrofuran
TLC	thin-layer chromatography

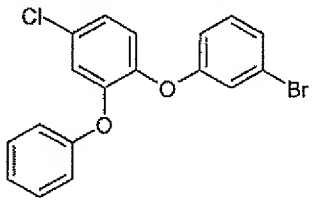
Example 1

{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenylsulfanyl}-acetic acid



Step A

1-(3-Bromo-phenoxy)-4-chloro-2-phenoxy-benzene



A solution of 4-chloro-2-phenoxy-phenol (1.65 g, 7.5 mmol), 1-bromo-3-iodobenzene (6.35 g, 22.4 mmol), copper(I) chloride (0.37 g, 3.74 mmol), 2,2,6,6-tetramethyl-3,5-heptanedione (0.345 g, 1.87 mmol), and cesium carbonate (2.93 g, 9 mmol) in NMP (20 mL) is heated to 120 °C. The reaction is stirred overnight and cooled to rt. The reaction is quenched with 1N aqueous HCL and extracted with ethyl ether. The organic is washed with brine, dried over sodium sulfate, filtered, and the solvent is removed. The crude is purified by silica gel column chromatography using 5/1 hexanes/ethyl acetate to elute the pure product. The solvent is removed to afford 1.13 g (40%) of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{18}H_{12}BrClO_2$ 374, found 375 and 377 (M + 1 and M + 3, 100%).

Step B

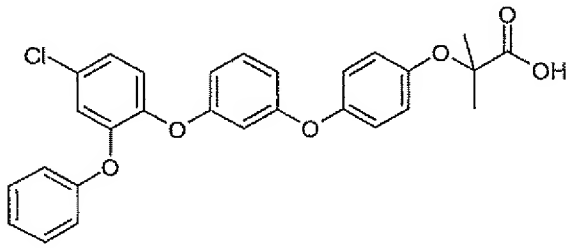
{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenylsulfanyl}-acetic acid

A solution of 1-(3-bromo-phenoxy)-4-chloro-2-phenoxy-benzene (0.15 g, 0.4 mmol), (4-hydroxy-2-methyl-phenylsulfanyl)-acetic acid ethyl ester (99 mg, 0.44 mmol), copper(I) chloride (20 mg, 0.2 mmol), 2,2,6,6-tetramethyl-3,5-heptanedione (0.02

mL, 0.1 mmol), and cesium carbonate (156 mg, 0.48 mmol) in NMP (3 mL) is heated to 120 °C. The reaction is stirred overnight and cooled to rt. The reaction is quenched with 1N aqueous HCl and extracted with ethyl ether. The organic is washed with brine, dried over sodium sulfate, and filtered. The solvent is removed to afford the crude ester intermediate. The intermediate is treated with 5N NaOH (0.4 mL, 2.2 mmol) in MeOH (5 mL) and heated to reflux. The reaction is stirred at reflux for 2 hours and then cooled. The reaction is quenched with 1N aqueous HCl to give pH=4. The aqueous layer is extracted with ethyl ether. The organic layer is washed with brine, dried over sodium sulfate, and filtered. The solvent is removed to afford the crude product. The crude is purified by prep HPLC to afford 78 mg (40%) of desired product. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{27}H_{21}ClO_5S$ 492, found 493 and 495 (M + 1 and M + 3, 100%).

Example 2

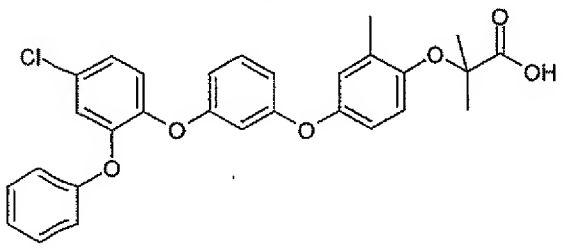
2-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-phenoxy}-2-methyl-propionic acid



The title compound is prepared according to Example 1, Step B by using 2-(4-hydroxy-phenoxy)-2-methyl-propionic acid ethyl ester to afford 63 mg (32%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{28}H_{23}ClO_6$ 490, found 491 and 493 (M+1 and M + 3, 100%).

Example 3

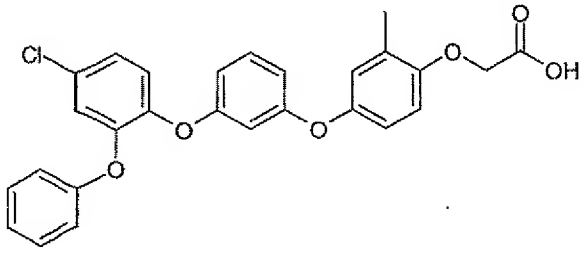
2-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid



The title compound is prepared according to Example 1, Step B by using 2-(4-hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester to afford 33 mg (16%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{25}ClO_6$ 504, found 505 and 507 (M + 1 and M + 3, 100%).

Example 4

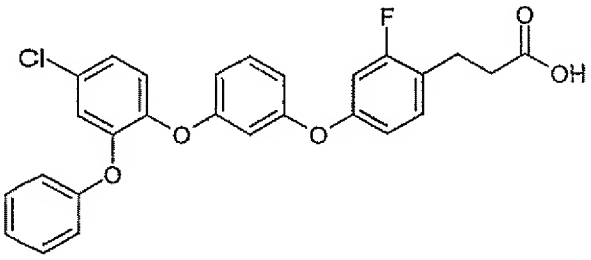
{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenoxy}-acetic acid



The title compound is prepared according to Example 1, Step B by using (4-hydroxy-2-methyl-phenoxy)-acetic acid ethyl ester to afford 30 mg (16%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^-) *m/z* mass calculated for $C_{27}H_{21}ClO_6$ 476, found 475 and 477 (M-1 and M + 1, 100%).

Example 5

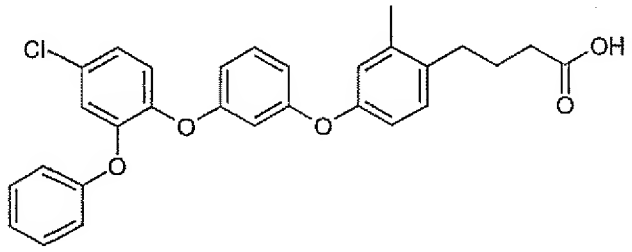
3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-fluoro-phenyl}-propionic acid



The title compound is prepared according to Example 1, Step B by using 3-(2-fluoro-4-hydroxy-phenyl)-propionic acid ethyl ester to afford 94 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{27}H_{20}ClFO_5$ 478, found 479 and 481 (M+1 and M + 3, 100%).

Example 6

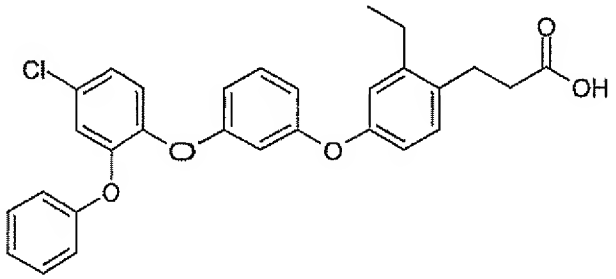
4-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-butyric acid



The title compound is prepared according to Example 1, Step B by using 4-(4-Hydroxy-2-methyl-phenyl)-butyric acid ethyl ester to afford 35 mg (18%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{25}ClO_5$ 488, found 487 and 489 (M - 1 and M + 1, 100%).

Example 7

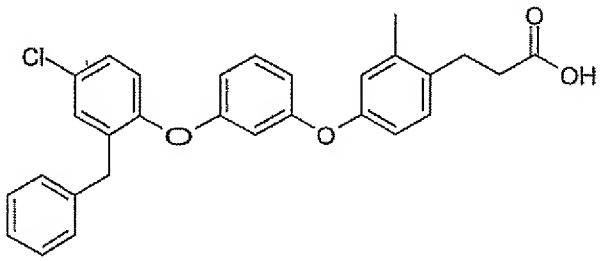
3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-ethyl-phenyl}-propionic acid



The title compound is prepared according to Example 1, Step B by using 3-(2-ethyl-4-hydroxy-phenyl)-propionic acid ethyl ester to afford 28 mg (16%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{25}ClO_5$ 488, found 489 and 491 (M + 1 and M + 3, 100%).

Example 8

3-{4-[3-(2-Benzyl-4-chloro-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid

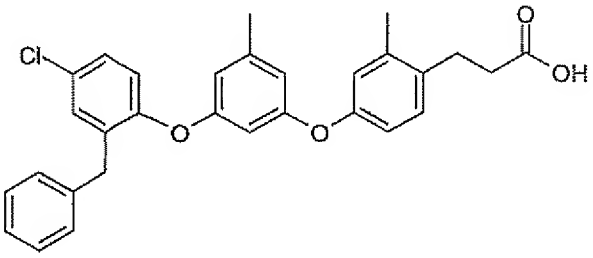


A solution of 3-[4-(3-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (0.1 g, 0.3 mmol), 2-benzyl-4-chloro-phenol (69 mg, 0.32 mmol), copper(I) chloride (14 mg, 0.14 mmol), 2,2,6,6-tetramethyl-3,5-heptanedione (0.01 mL, 0.07 mmol), and cesium carbonate (113 mg, 0.35 mmol) in NMP (3 mL) is heated to 120 °C. The reaction is stirred overnight and cooled to rt. The reaction is then quenched with 1N aqueous HCl and extracted with ethyl ether. The organic is washed with brine, dried over sodium sulfate, and filtered. The solvent is removed to afford the crude ester intermediate. The intermediate is treated with 5N NaOH (0.4 mL, 2.2 mmol) in MeOH (5 mL) and heated to reflux. The reaction is stirred at reflux for 2 hours and then cooled. The reaction is quenched with 1N aqueous HCl to obtain pH=4. The aqueous layer is extracted with ethyl ether. The organic layer is washed with brine, dried over sodium

sulfate, and filtered. The solvent is removed to afford the crude product. The crude is purified by prep HPLC to afford 63 mg (47%) of desired product. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{25}ClO_4$ 472, found 473 and 475 (M + 1 and M + 3, 100%).

Example 9

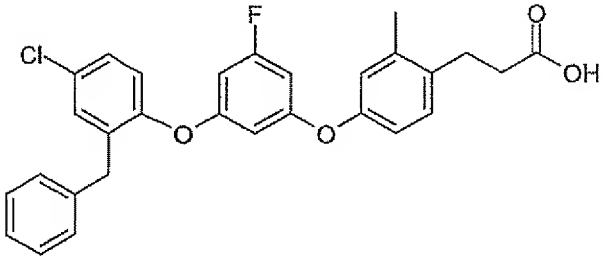
3-{4-[3-(2-Benzyl-4-chloro-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 8 by using 3-[4-(3-bromo-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester to afford 63 mg (48%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{30}H_{27}ClO_4$ 486, found 487 and 489 (M + 1 and M + 3, 100%).

Example 10

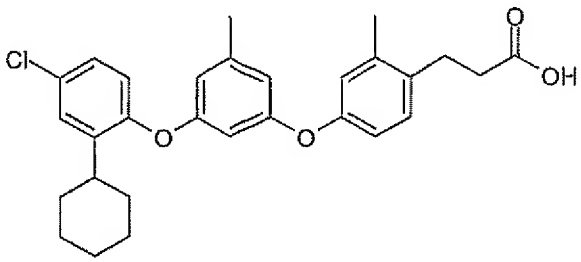
3-{4-[3-(2-Benzyl-4-chloro-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 8 by using 3-[4-(3-Bromo-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester to afford 54 mg (41%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{24}ClFO_4$ 490, found 491 and 493 (M + 1 and M + 3, 100%).

Example 11

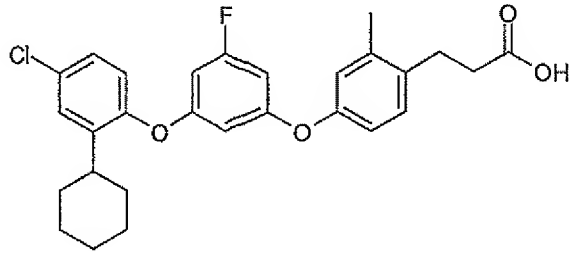
3-{4-[3-(4-Chloro-2-cyclohexyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid



A solution of 3-[4-(3-bromo-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (0.1 g, 0.27 mmol), 4-chloro-2-cyclohexyl-phenol (63 mg, 0.3 mmol), copper(I) chloride (13 mg, 0.13 mmol), 2,2,6,6-tetramethyl-3,5-heptanedione (0.01 mL, 0.07 mmol), and cesium carbonate (105 mg, 0.32 mmol) in NMP (3 mL) is heated to 120 °C. The reaction is stirred overnight and cooled to rt. The reaction is quenched with 1N aqueous HCl and extracted with ethyl ether. The organic layer is washed with brine, dried over sodium sulfate, and filtered. The solvent is removed to afford the crude ester intermediate. The intermediate is treated with 5N NaOH (0.4 mL, 2.2 mmol) in MeOH (5 mL) and heated to reflux. The reaction stirred at reflux for 2 hours and then cooled. The reaction is quenched with 1N aqueous HCl to obtain pH=4. The aqueous layer is extracted with ethyl ether. The organic layer is washed with brine, dried over sodium sulfate, and filtered. The solvent is removed to afford the crude product. The crude is purified by HPLC to afford 49 mg (38%) of desired product. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{31}ClO_4$ 478, found 479 and 481 (M + 1 and M + 3, 100%).

Example 12

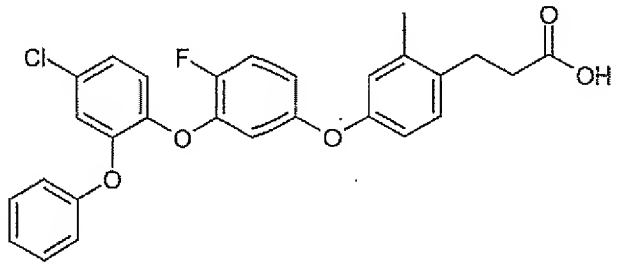
3-{4-[3-(4-Chloro-2-cyclohexyl-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 8 by using 3-[4-(3-Bromo-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester to afford 25 mg (19%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{28}H_{28}ClFO_4$ 482, found 483 and 485 (M + 1 and M + 3, 100%).

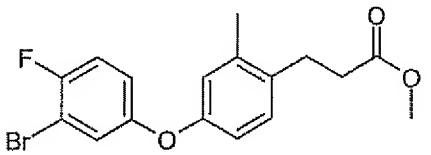
Example 13

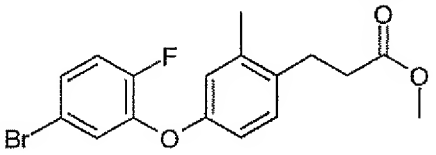
3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-4-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid



Step A

3-[4-(3-Bromo-4-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester and 3-[4-(5-Bromo-2-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



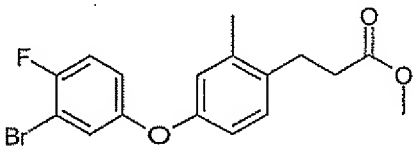


A solution of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (10 g, 52 mmol), 2,4-dibromofluorobenzene (19.6 g, 77.2 mmol), copper(I) chloride (2.54 g, 25.7 mmol), 2,2,6,6-tetramethyl-3,5-heptanedione (2.65 mL, 12.9 mmol), and cesium

carbonate (20 g, 61.8 mmol) in NMP (150 mL) is heated to 120 °C. The reaction is stirred overnight and cooled to rt. The reaction is then quenched with 1N aqueous HCl and extracted with ethyl ether. The organic layer is washed with brine, dried over sodium sulfate, filtered, and the solvent is removed. The crude is purified by silica gel column chromatography using 9/1 hexanes/acetone to elute the pure product. The solvent is removed to afford 4.36 g (23%) of the two desired products. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{17}H_{16}BrFO_3$ 366, found 367 (M + 1, 100%).

Step B

3-[4-(3-Bromo-4-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



The mixture from Step A (1.0 g) is separated by prep HPLC to afford 0.29 g (29%) of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{17}H_{16}BrFO_3$ 366, found 367 (M + 1, 100%).

Step C

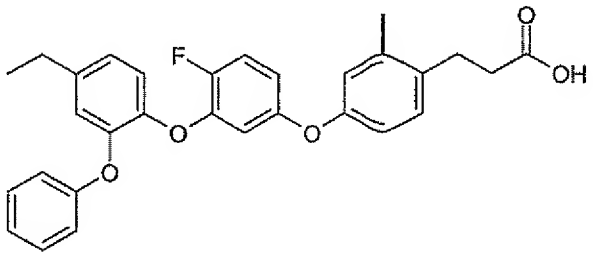
3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-4-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid

A solution of 3-[4-(3-bromo-4-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (0.1 g, 0.27 mmol), 4-chloro-2-phenoxy-phenol (60 mg, 0.27 mmol), copper(I) chloride (13 mg, 0.13 mmol), 2,2,6,6-tetramethyl-3,5-heptanedione (0.01 mL, 0.07 mmol), and cesium carbonate (105 mg, 0.32 mmol) in NMP (3 mL) is heated to 120 °C. The reaction is stirred overnight and cooled to rt. The reaction is then quenched with 1N aqueous HCl and extracted with ethyl ether. The organic layer is washed with brine, dried over sodium sulfate, and filtered. The solvent is removed to afford the crude ester intermediate. The intermediate is treated with 5N NaOH (0.4 mL, 2.2 mmol) in MeOH (5 mL) and heated to reflux. The reaction is stirred at reflux for 2 hours and then cooled. The reaction is quenched with 1N aqueous HCl to obtain pH=4. The aqueous layer is extracted with ethyl ether. The organic layer is washed with brine, dried over sodium sulfate, and filtered. The solvent is removed to afford the crude product. The crude is purified by prep HPLC to afford 15 mg (11%) of desired product.

^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{28}H_{22}ClFO_5$ 492, found 493 and 495 (M + 1 and M + 3, 100%).

Example 14

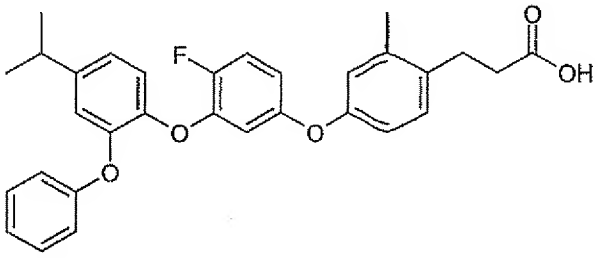
3-{4-[3-(4-Ethyl-2-phenoxy-phenoxy)-4-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 13, Step C by using 4-ethyl-2-phenoxy-phenol to afford 20 mg (15%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{30}H_{27}FO_5$ 486, found 487 (M + 1, 100%).

Example 15

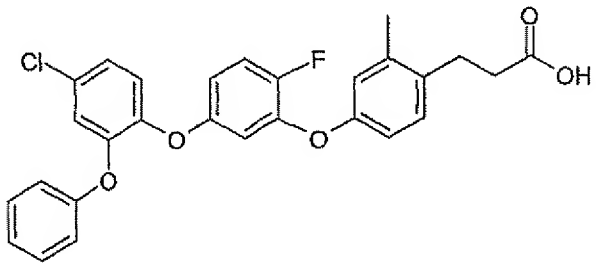
3-{4-[3-(4-Isopropyl-2-phenoxy-phenoxy)-4-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 13, Step C by using 4-isopropyl-2-phenoxy-phenol to afford 9 mg (7%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{31}H_{29}FO_5$ 500, found 501 (M + 1, 100%).

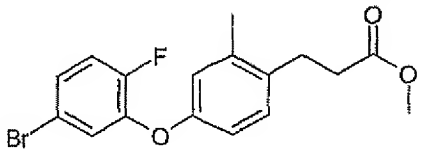
Example 16

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-4-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid



Step A

3-[4-(5-Bromo-2-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



The mixture from Example 13, Step A (1.0 g) is separated by prep HPLC to afford 0.195 g (20%) of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{17}H_{16}BrFO_3$ 366, found 367 (M + 1, 100%).

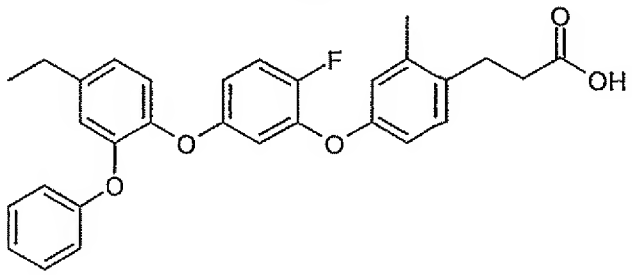
Step B

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-4-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid

The title compound is prepared according to Example 13, Step C by using 3-[4-(5-bromo-2-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester to afford 2.9 mg (2%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{28}H_{22}ClFO_5$ 492, found 493 and 495 (M + 1 and M + 3, 100%).

Example 17

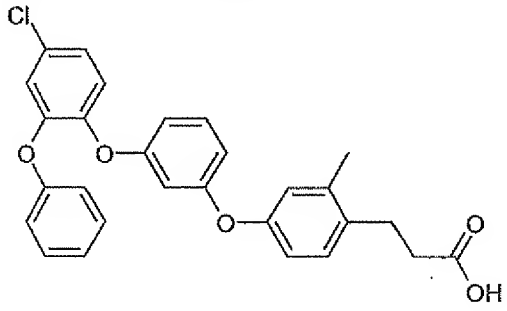
3-{4-[5-(4-Ethyl-2-phenoxy-phenoxy)-2-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 13, Step C by using 3-[4-(5-bromo-2-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester and 4-ethyl-2-phenoxy-phenol to afford 15 mg (11%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{30}H_{27}FO_5$ 486, found 487 (M + 1, 100%).

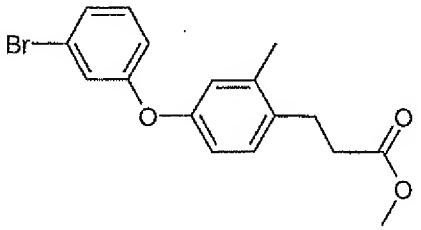
Example 18

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



Step A

3-[4-(3-Bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

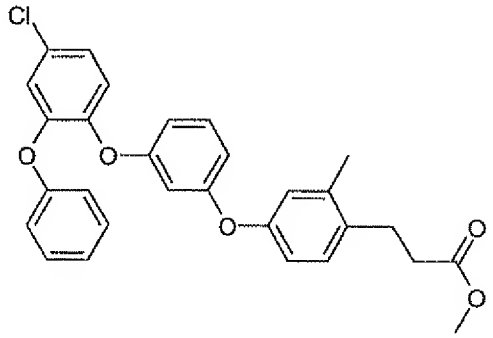


A mixture of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (4.0 g, 20.6 mmol), 1-bromo-3-iodobenzene (17.49 g, 61 .8 mmol), cesium carbonate (8.05 g, 24.7 mmol), copper (I) chloride (1.02 g, 10.3 mmol) and 2,2,6,6-tetramethyl-3,5-

heptanedione (0.95 g, 5.15 mmol) in 1-methyl-2-pyrrolidinone (40 mL) is heated to 120 ^{0}C for 17 hours under N_2. The reaction is cooled and quenched with 1 N HCl (50 mL). The mixture is then diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 4.30 g (60%) of the title compound. R_f = 0.33 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{17}H_{17}O_3Br$ 348, found 349 and 351 (M +1 and M + 3, 100%).

Step B

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester



A mixture of 3-[4-(3-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (0.474 g, 1.36 mmol), 4-chloro-2-phenoxy-phenol (0.30 g, 1.36 mmol), cesium carbonate (0.531 g, 1.63 mmol), copper (I) chloride (0.067 g, 0.677 mmol) and 2,2,6,6-tetramethyl-3,5-heptanedione (0.063 g, 0.342 mmol) in 1-methyl-2-pyrrolidinone (5 mL) is heated to 120 ^{0}C for 20 hours under N_2. The reaction is cooled and quenched with 1 N HCl (20 mL). The mixture is then diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 0.221 g (33%) of the title compound. R_f = 0.29 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{25}O_5Cl$ 488, found 489 and 351 (M + 1 and M + 3, 100%).

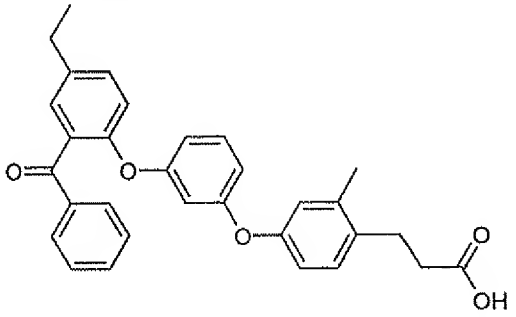
Step C

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid

A solution of 3-{4-[3-(4-chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (0.221, 0.452 mmol) in methanol (7 mL) is treated with 5 N NaOH (2 mL) and heated to reflux until saponification is completed. The mixture is cooled, and the solvent is removed *in vacuo* to afford a residue that is acidified with 1 N HCl. The mixture is diluted with water and extracted with ethyl acetate. The organic layer is dried (Na_2SO_4), and the solvent removed *in vacuo* to afford 0.230 g (100%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{28}H_{23}O_5Cl$ 474, found 475 and 477 (M + 1 and M + 3, 100%).

Example 19

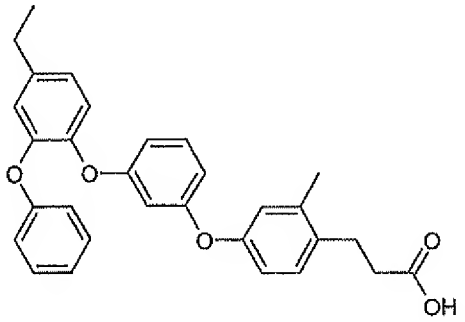
3-{4-[3-(2-Benzoyl-4-ethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with (5-ethyl-2-hydroxy-phenyl)-phenyl-methanone as in Example 18 to afford 0.220 g (50%). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{31}H_{28}O_5$ 481.2015, found 481.2032 (M + 1).

Example 20

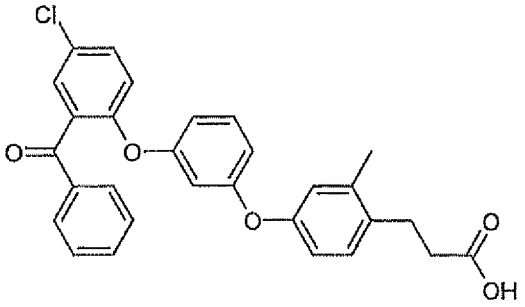
3-{4-[3-(4-Ethyl-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 4-ethyl-2-phenoxy-phenol as in Example 18 to afford 0.200 g (35%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{30}H_{28}O_5$ 468, found 469 (M + 1, 100%).

Example 21

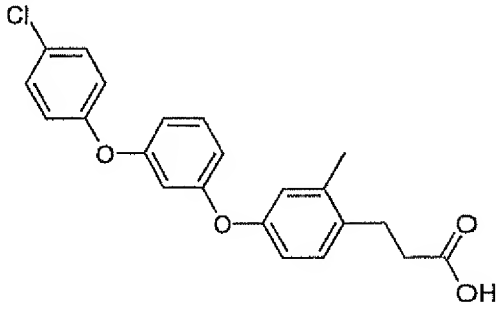
3-{4-[3-(2-Benzoyl-4-chloro-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with (5-chloro-2-hydroxy-phenyl)-phenyl-methanone as in Example 18 to afford 0.080 g. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{23}O_5Cl$ 486, found 487 and 489 (M + 1 and M + 3, 100%).

Example 22

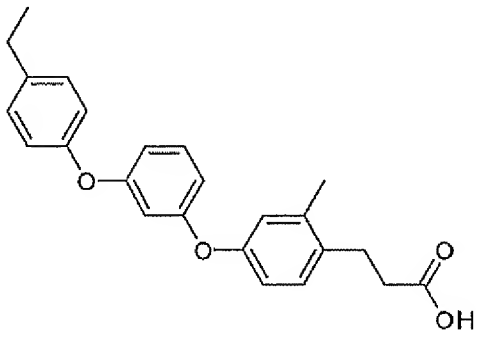
3-{4-[3-(4-Chloro-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 4-chlorophenol as in Example 18 to afford 0.019 g (9%). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{22}H_{19}O_4Cl$ 383.1050, found 383.1033 (M + 1).

Example 23

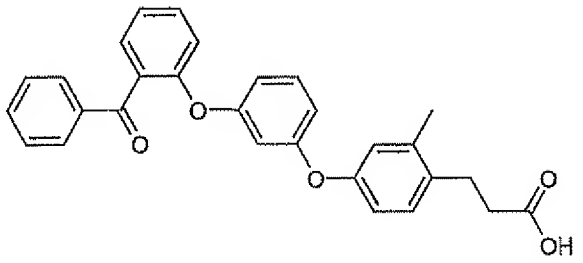
3-{4-[3-(4-Ethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 4-ethylphenol as in Example 18 to afford 0.020 g (14%). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{24}H_{24}O_4$ 377.1753, found 377.1747.

Example 24

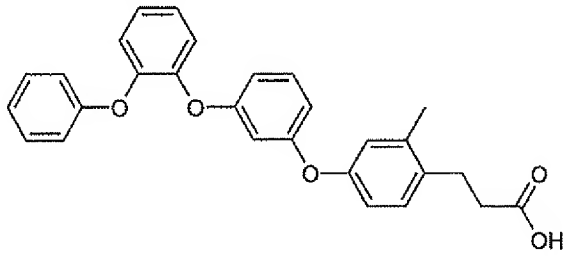
3-{4-[3-(2-Benzoyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with (2-hydroxy-phenyl)-phenyl-methanone as in Example 18 to afford 0.020 g (14%). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* mass calculated for $C_{29}H_{24}O_5$ 453.1702, found 453.1699.

Example 25

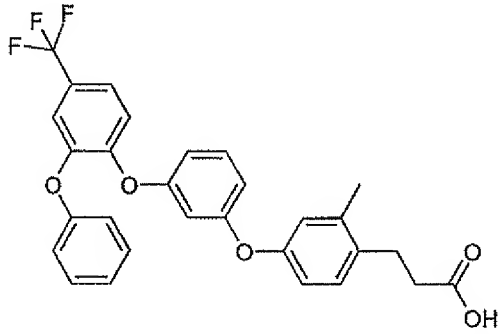
3-{2-Methyl-4-[3-(2-phenoxy-phenoxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 2-phenoxy-phenol as in Example 18 to afford 0.106 g (42%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{28}H_{24}O_5$ 440, found 441 (M + 1).

Example 26

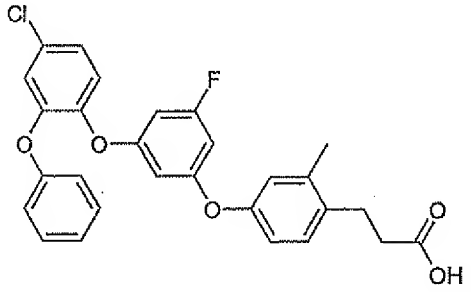
3-{2-Methyl-4-[3-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(5-bromo-pyridin-3-yloxy)-2-methyl-phenyl]-propionic acid methyl ester with 2-phenoxy-4-trifluoromethyl-phenol as in Example 18 to afford 0.084 g (15%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^-) *m/z* mass calculated for $C_{29}H_{23}O_5F_3$ 508, found 507 (M - 1).

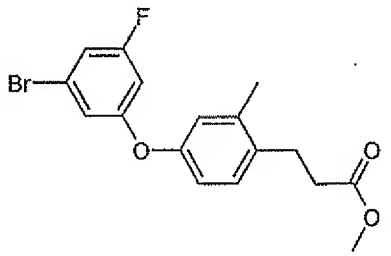
Example 27

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid



Step A

3-[4-(3-Bromo-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



A mixture of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (4.0 g, 20.6 mmol), 1,3-dibromo-5-fluorobenzene (15.71 g, 61.9 mmol), cesium carbonate (8.05 g, 24.7 mmol), copper (I) chloride (1.02 g, 10.3 mmol) and 2,2,6,6-tetramethyl-3,5-heptanedione (0.95 g, 5.15 mmol) in 1-methyl-2-pyrrolidinone (40 mL) is heated to 120 ^{0}C for 7 hours under N_2. The reaction is cooled and quenched with 1 N HCl (40 mL). The mixture is then diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 3.43 g (45%) of the title compound. R_f = 0.38 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{17}H_{16}O_3BrF$ 366, found 384 and 386 (M + NH_4, 100%).

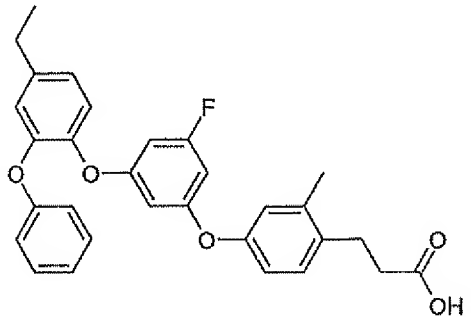
Step B

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid

The title compound is prepared by reacting the compound of 3-[4-(3-bromo-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 4-chloro-2-phenoxy-phenol as in Example 18 to afford 0.118 g (22%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{28}H_{22}O_5ClF$ 492, found 493 and 495 (M+1 and M+3).

Example 28

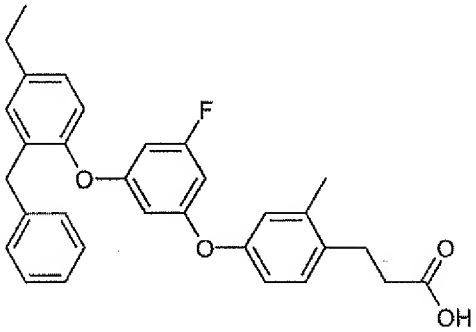
3-{4-[3-(4-Ethyl-2-phenoxy-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 4-ethyl-2-phenoxy-phenol as in Example 18 to afford 0.139 g (52%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^-) *m/z* mass calculated for $C_{30}H_{27}O_5F$ 486, found 485 (M - 1).

Example 29

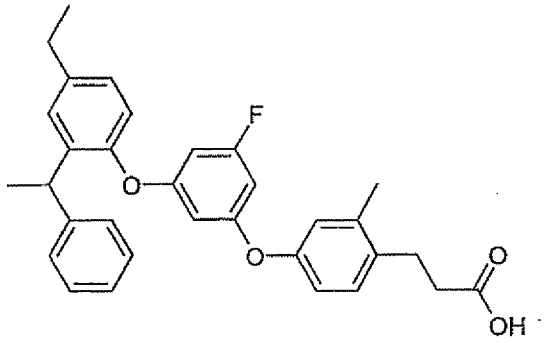
3-{4-[3-(2-Benzyl-4-ethyl-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 2-benzyl-4-ethyl-phenol as in Example 18 to afford 0.040 g (13%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{31}H_{29}O_4F$ 484, found 485 (M + 1, 100%).

Example 30

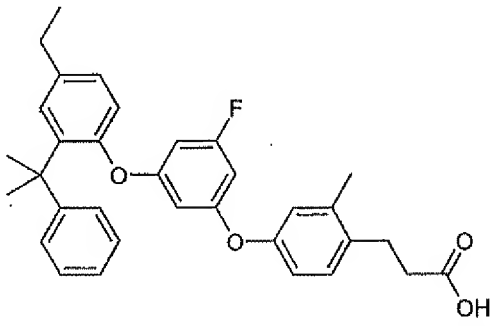
3-(4-{3-[4-Ethyl-2-(1-phenyl-ethyl)-phenoxy]-5-fluoro-phenoxy}-2-methyl-phenyl)-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 4-ethyl-2-(1-phenyl-ethyl)-phenol as in Example 18 to afford 0.078 g (29%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{32}H_{31}O_4F$ 498, found 499 (M + 1, 100%).

Example 31

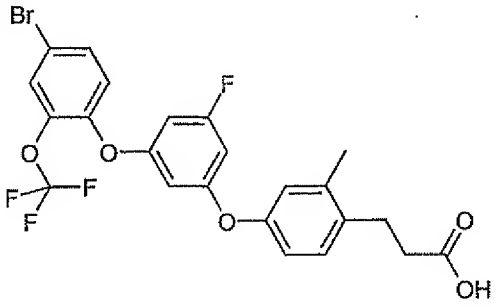
3-(4-{3-[4-Ethyl-2-(1-methyl-1-phenyl-ethyl)-phenoxy]-5-fluoro-phenoxy}-2-methyl-phenyl)-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 4-ethyl-2-(1-methyl-1-phenyl-ethyl)-phenol as in Example 18 to afford 0.027 g (10%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{33}H_{33}O_4F$ 512, found 513 (M + 1, 100%).

Example 32

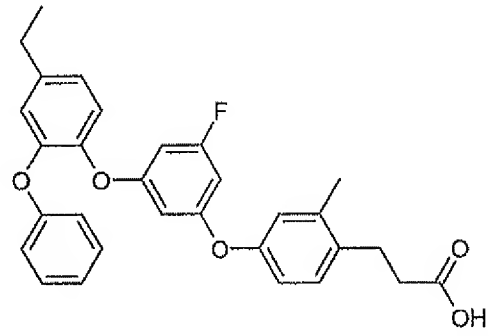
3-{4-[3-(4-Bromo-2-trifluoromethoxy-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 4-bromo-2-trifluoromethoxy-phenol as in Example 18 to afford 0.013 g (5%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{23}H_{17}O_5F_4Br$ 528, found 529 (M + 1, 100%).

Example 33

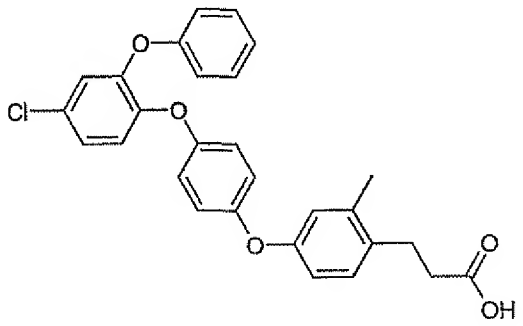
3-{4-[3-(4-Ethyl-2-phenoxy-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 4-ethyl-2-phenoxy-phenol as in Example 18 to afford 0.139 g (52%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{30}H_{27}O_5F$ 487.1921, found 487.1906.

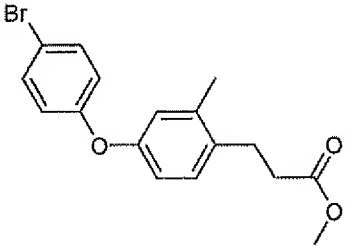
Example 34

3-{4-[4-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



Step A

3-[4-(4-Bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



A mixture of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (2.0 g, 10.3 mmol), 1-bromo-4-iodobenzene (8.74 g, 30.9 mmol), cesium carbonate (4.03 g, 12.4 mmol), copper (I) chloride (0.51 g, 5.15 mmol) and 2,2,6,6-tetramethyl-3,5-heptanedione (0.47 g, 2.55 mmol) in 1-methyl-2-pyrrolidinone (20 mL) is heated to 120 ^{0}C for 1 hour under N_2. The reaction is cooled and quenched with 1 N HCl. The mixture is then diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 1.51 g (42%) of the title compound. R_f = 0.35 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$).

Step B

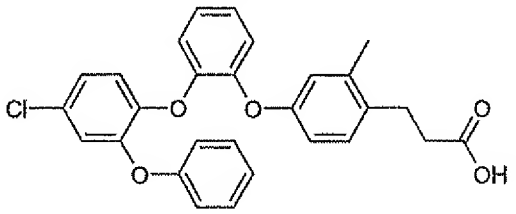
3-{4-[4-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid

The title compound is prepared by reacting the compound of 3-[4-(4-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 4-chloro-2-phenoxy-

phenol as in Example 18 to afford 0.133 g (19%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^-) *m/z* mass calculated for $C_{28}H_{23}O_5Cl$ 474, found 473 and 475 (M – 1, and M + 1, 100%).

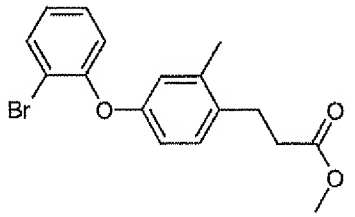
Example 35

3-{4-[2-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



Step A

3-[4-(2-Bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



A mixture of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (2.0 g, 10.3 mmol), 1-bromo-2-iodobenzene (8.74 g, 30.9 mmol), cesium carbonate (4.03 g, 12.4 mmol), copper (I) chloride (0.51 g, 5.15 mmol) and 2,2,6,6-tetramethyl-3,5-heptanedione (0.47 g, 2.55 mmol) in 1-methyl-2-pyrrolidinone (20 mL) is heated to 120 ^{0}C for 10 hours under N_2. The reaction is cooled and quenched with 1 N HCl. The mixture is then diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 1.09 g (30%) of the title compound. R_f = 0.34 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$).

Step B

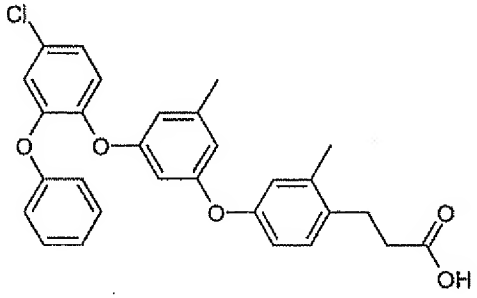
3-{4-[2-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid

The title compound is prepared by reacting the compound of 3-[4-(2-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 4-chloro-2-phenoxy-

phenol as in Example 18 to afford 0.039 g (8%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^-) *m/z* mass calculated for $C_{28}H_{23}O_5Cl$ 474, found 473 and 475 (M – 1, and M + 1).

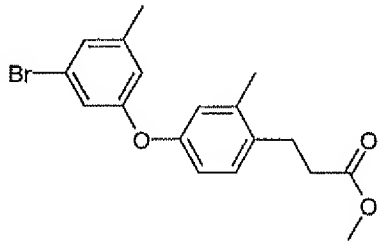
Example 36

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid



Step A

3-[4-(3-Bromo-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



The mixture of 1,3-dibromo-5-methyl-benzene (15 g, 0.06 mol), 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (3.9 g, 0.02 mol), CuCl (1 g, 0.01 mol), 2,2,6,6-tetramethyl-heptane-3,5-dione (0.92 g, 0.005 mol) and Cs2CO3 (7.8 g, 0.024 mol) in 40 mL of dry NMP is heated to 120oC for overnight. The mixture is cooled to rt and diluted with Et_2O and filtered through a pad of celite. Organic layer is washed with 1N HCl, H_2O and brine, and then dried over Na_2SO_4, filtered and concentrated. Crude material is purified by chromatography (hexanes/acetone = 20:1) to afford the title compound (59%) as a yellow oil. R_f = 0.29 (20/1 hexanes/acetone). ^{1}H NMR (400 MHz, $CDCl_3$).

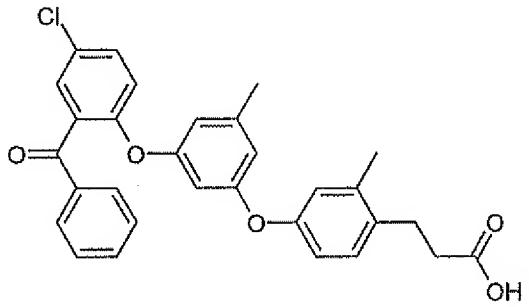
Step B

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid

The title compound is prepared by reacting the compound of 3-[4-(3-bromo-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with 4-chloro-2-phenoxy-phenol as in Example 18 to afford 0.118 g (22%). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{29}H_{25}O_5Cl$ 489.1469, found 489.1457.

Example 37

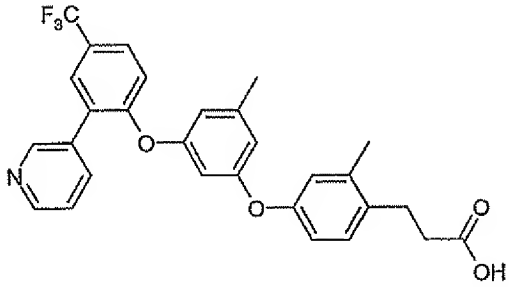
3-{4-[3-(2-Benzoyl-4-chloro-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-[4-(3-bromo-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester with (5-chloro-2-hydroxy-phenyl)-phenyl-methanone as in Example 18 to afford 0.244 g (38%). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{30}H_{25}O_5Cl$ 501.1469, found 501.1474.

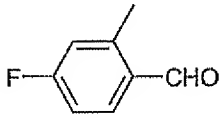
Example 38

3-{2-Methyl-4-[3-methyl-5-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



Step A

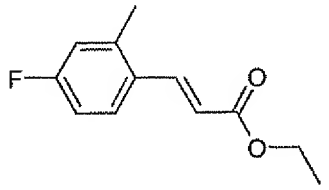
4-Fluoro-2-methyl-benzaldehyde



A -78 ^{0}C solution of 2-bromo-5-fluorotoluene (12.0 g, 63.5 mmol) in dry THF (60 mL) is treated with a 1.6 M hexanes solution of *n*-butyl lithium (59.5 mL, 95.3 mmol) and then stirred for 15 minutes at – 78 ^{0}C under N_2. The mixture is then treated with DMF (27.8 g, 0.381 mol) and warmed to rt. The reaction is acidified with 1 N HCl, diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using a gradient of 5/1 to 3/1 to hexanes/ethyl acetate to afford 6.24 g (71%) of the title compound. R_f = 0.49 (2/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$).

Step B

3-(4-Fluoro-2-methyl-phenyl)-acrylic acid ethyl ester

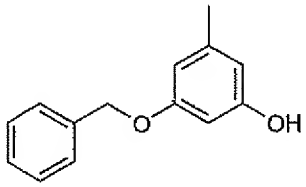


A mixture of 4-fluoro-2-methyl-benzaldehyde (1.16 g, 8.40 mmol), triethyl phosphonoacetate (2.26 g, 10.1 mmol), and 325 mesh potassium carbonate (3.48

g, 25.2 mmol) in ethanol (15 mL) is heated to reflux for 5 hours under N_2. The reaction is cooled, filtered and the filtrate is acidified with 1 N HCl. The mixture is then diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4, and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 6/1 hexanes/ethyl acetate to afford 1.21 g (69%) of the title compound. R_f = 0.58 (2/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{12}H_{13}O_2F$ 208, found 209 (M + 1, 100%).

Step C

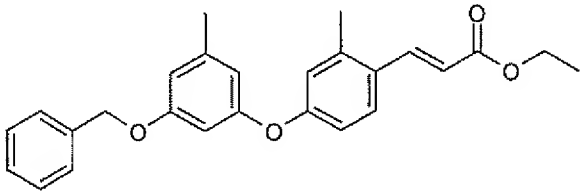
3-Benzyloxy-5-methyl-phenol



A 0 ^{0}C mixture of orcinol (10.0 g, 80.6 mmol) and 325 mesh potassium carbonate (12.25 g, 88.6 mmol) in DMF (100 mL) is treated dropwise with benzyl bromide (6.91 g, 40.4 mmol). The mixture was then warmed to rt and stirred for 20 hours under N_2. The reaction is filtered, and the filtrate is acidified with 1 N HCl. The mixture is then diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 5/1 hexanes/ethyl acetate to afford 4.88 g (57%) of the title compound. R_f = 0.40 (2/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{14}H_{14}O_2$ 214, found 215 (M + 1, 100%).

Step D

3-[4-(3-Benzyloxy-5-methyl-phenoxy)-2-methyl-phenyl]-acrylic acid ethyl ester

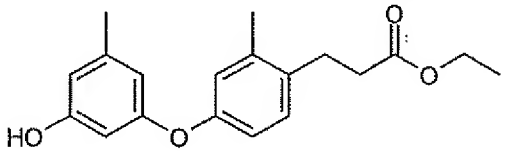


A mixture of 3-benzyloxy-5-methyl-phenol (3.24 g, 15.1 mmol), 3-(4-fluoro-2-methyl-phenyl)-acrylic acid ethyl ester (3.15 g, 15.1 mmol) and 325 mesh potassium carbonate (2.51 g, 18.2 mmol) in dry DMSO (40 mL) is heated to 130 ^{0}C and

stirred for 20 hours under N_2. The reaction is cooled and acidified with 1 N HCl (30 mL). The mixture is then diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 3.56 g (58%) of the title compound. R_f = 0.39 (4/1 hexanes/EtOAc). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{26}H_{26}O_4$ 402, found 403 (M + 1, 100%).

Step E

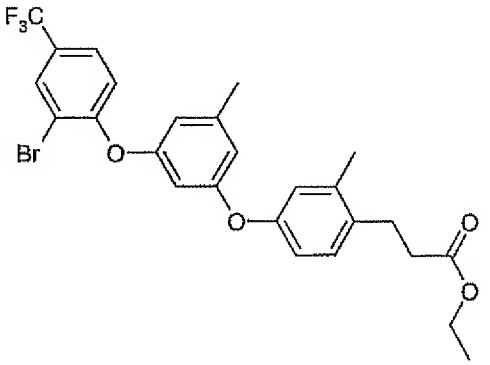
3-[4-(3-Hydroxy-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester



A mixture of 3-[4-(3-benzyloxy-5-methyl-phenoxy)-2-methyl-phenyl]-acrylic acid ethyl ester (3.56 g, 88.5 mmol) and 10% Pd/C (1.75 g) in ethyl acetate (90 mL) is purged with N_2, then purged with H_2 and stirred under a hydrogen balloon. Upon completion, the mixture is filtered through hyflo, and the solvent is removed *in vacuo* to afford 2.83 g (100%) the title compound. R_f = 0.35 (2/1 hexanes/EtOAc). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{19}H_{22}O_4$ 314, found 315 (M+1, 100%).

Step F

3-{4-[3-(2-Bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester

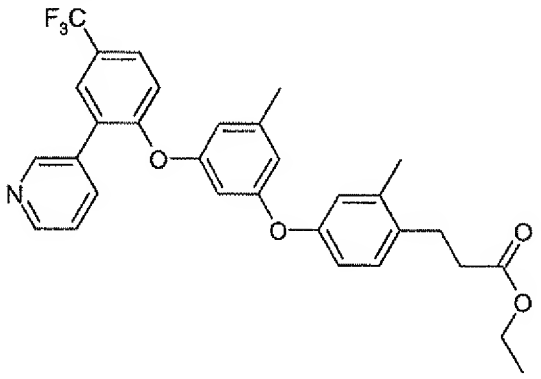


A mixture of 3-[4-(3-hydroxy-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester (2.83 g, 9.01 mmol), 3-bromo-4-fluorobenzotrifluoride (2.19 g, 9.01 mmol) and 325 mesh potassium carbonate (1.49 g, 10.8 mmol) in dry DMSO (36

mL) is heated to 100 ^{0}C and stirred for 5 hours under N_2. The reaction is cooled and acidified with 1 N HCl. The mixture is then diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 3.45 g (71%) of the title compound. R_f = 0.54 (2/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{26}H_{24}O_4F_3Br$ 536, found 554 and 556 (M + NH_4, 100%).

Step G

3-{2-Methyl-4-[3-methyl-5-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid ethyl ester



A mixture of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester (0.112 g, 0.209 mmol), pyridine-3-boronic acid (0.077 g, 0.626 mmol), and cesium fluoride (0.111 g, 0.731 mmol) in dry ACN (7 mL) is purged with N_2 and then treated with 1,1'-bis(diphenylphophino)-ferrocene palladium (II) chloride complex with DCM (0.031 g, 0.042 mmol). The mixture is heated to 100 ^{0}C and stirred for 5 hours under N_2. The reaction is cooled, and the crude mixture is absorbed on silica gel and purified by flash chromatography using 2/1 hexanes/ethyl acetate to afford 0.089 g (79%) of the title compound. R_f = 0.33 (1/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{31}H_{28}O_4NF_3$ 535, found 536 (M +1, 100%).

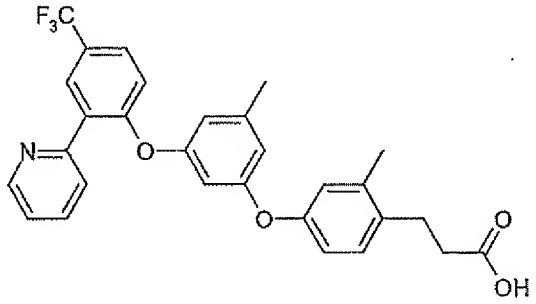
Step H

3-{2-Methyl-4-[3-methyl-5-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

A solution of 3-{2-methyl-4-[3-methyl-5-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid ethyl ester (0.089, 0.166 mmol) in ethanol (7 mL) is treated with 5 N NaOH (2 mL) and heated to until saponification is completed. The mixture is cooled, and the solvent is removed *in vacuo* to afford a residue that is neutralized with 1 N HCl. The mixture is diluted with water and extracted with ethyl acetate. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford 0.093 g (100%) of the title compound. ^1H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{29}H_{24}O_4F_3N$ 508.1736, found 508.1724.

Example 39

3-{2-Methyl-4-[3-methyl-5-(2-pyridin-2-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

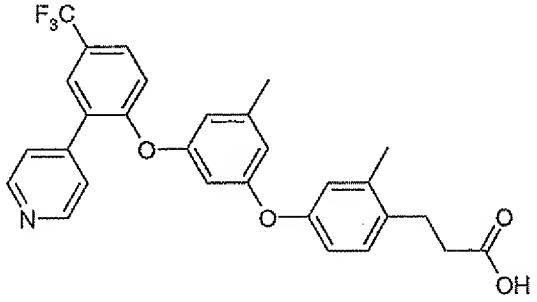


A mixture of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester (0.155 g, 0.289 mmol) and 2-tributylstannyl pyridine (0.210 g, 0.571 mmol) in dry toluene (8 mL) is purged with N_2 and then tetrakis(triphenylphospine)pallium (0) (0.033 g, 0.029 mmol) is added. The reaction is heated to 100 ^{0}C and stirred for 20 hours under N_2. The reaction is cooled, and the solvent is removed *in vacuo* to give crude 3-{2-methyl-4-[3-methyl-5-(2-pyridin-2-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid ethyl ester. This ester is dissolved in ethanol (8 mL), treated with 5 N NaOH (2 mL) and heated to reflux until saponification is complete. The mixture is cooled, and the solvent is removed *in vacuo* to

afford a residue that is acidified with 1 N HCl. The mixture is diluted with water and extracted with ethyl acetate. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to give crude product that is purified by preparative HPLC to afford 0.056 g (38%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{24}NO_4F_3$ 507, found 508 (M + 1, 100%).

Example 40

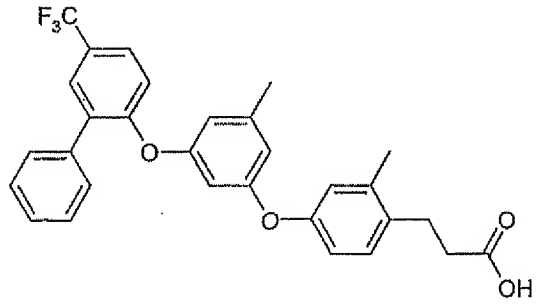
3-{2-Methyl-4-[3-methyl-5-(2-pyridin-4-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with 4-pyridyl boronic acid as in Example 38 to afford 0.011 g (9%). ^{1}HNMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{24}NO_4F_3$ 507, found 508 (M+1, 100%).

Example 41

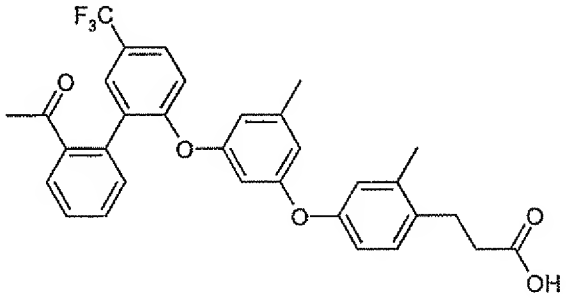
3-{2-Methyl-4-[3-methyl-5-(5-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with phenyl boronic acid as in Example 38 to afford 0.024 g (21%). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{30}H_{26}O_4F_3$ 507.1783, found 507.1797.

Example 42

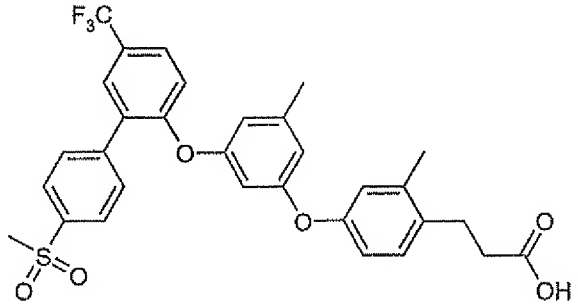
3-{4-[3-(2'-Acetyl-5-trifluoromethyl-biphenyl-2-yloxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with 2-acetyl phenyl boronic acid as in Example 38 to afford 0.032 g (28%). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{32}H_{28}O_5F_3$ 549.1888, found 549.1870.

Example 43

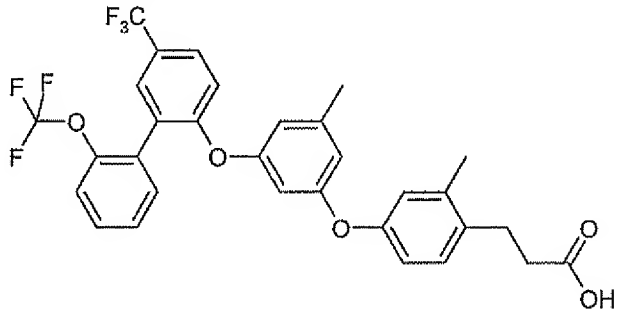
3-{4-[3-(4'-Methanesulfonyl-5-trifluoromethyl-biphenyl-2-yloxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with 4-(methylsulfonyl)phenyl boronic acid as in Example 38 to afford 0.062 g (48%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{31}H_{27}O_6SF_3$ 584, found 585 (M + 1, 100%).

Example 44

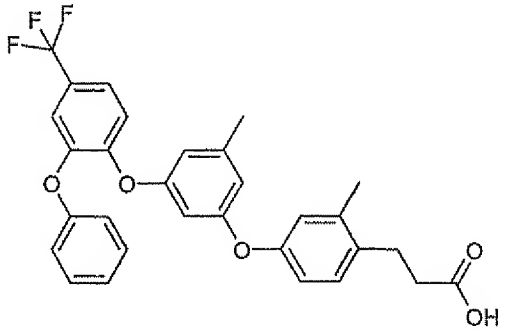
3-{2-Methyl-4-[3-methyl-5-(2'-trifluoromethoxy-5-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with 2-trifluoromethoxyphenyl boronic acid as in Example 38 to afford 0.058 g (39%). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{31}H_{25}O_5F_6$ 591.1606, found 591.1619.

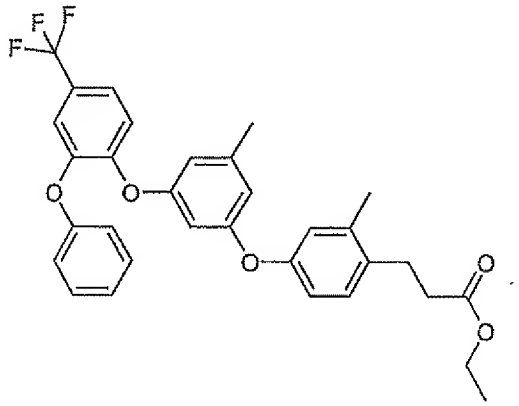
Example 45

3-{2-Methyl-4-[3-methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



Step A

3-{2-Methyl-4-[3-methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid ethyl ester



A mixture of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester (0.309 g, 0.576 mmol), phenol (0.163 g, 1.73 mmol), cesium carbonate (0.56 g, 1.72 mmol), copper (I) chloride (0.029 g, 0.293 mmol) and 2,2,6,6-tetramethyl-3,5-heptanedione (0.027 g, 0.147 mmol) in 1-methyl-2-pyrrolidinone (10 mL) is heated to 120 ^{0}C for 20 hours under N_2. The reaction is cooled and quenched with 1 N HCl (20 mL). The mixture is then diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 0.173 g (43%) of the title compound. R_f = 0.55 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{32}H_{29}O_{35}F_3$ 550, found 551 (M +1, 100%).

Step B

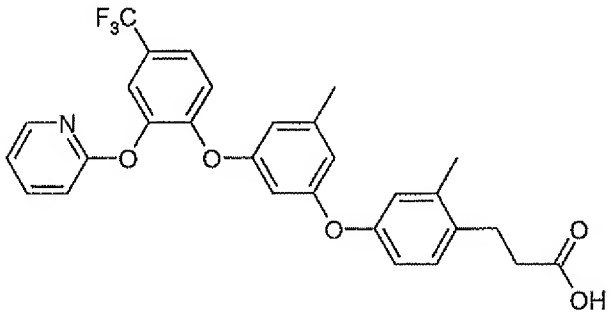
3-{2-Methyl-4-[3-methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

A solution of 3-{2-methyl-4-[3-methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid ethyl ester (0.137, 0.249 mmol) in ethanol (8 mL) is treated with 5 N NaOH (2 mL) and heated to reflux until saponification is completed. The mixture is cooled, and the solvent is removed *in vacuo* to afford a residue that is acidified with 1 N HCl. The mixture is diluted with water and extracted with ethyl acetate. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to

afford 0.143 g (100%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{30}H_{25}O_5F_3$ 523.1732, found 523.1721.

Example 46

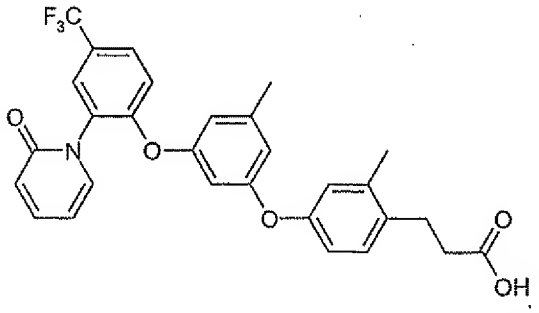
3-(2-Methyl-4-{3-methyl-5-[2-(pyridin-2-yloxy)-4-trifluoromethyl-phenoxy]-phenoxy}-phenyl)-propionic acid



The title compound is prepared by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with 2-hydroxypyridine as in Example 45 to afford 0.015 g (10%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{24}NO_5F_3$ 523, found 524 (M+1, 100%).

Example 47

3-(2-Methyl-4-{3-methyl-5-[2-(2-oxo-2H-pyridin-1-yl)-4-trifluoromethyl-phenoxy]-phenoxy}-phenyl)-propionic acid

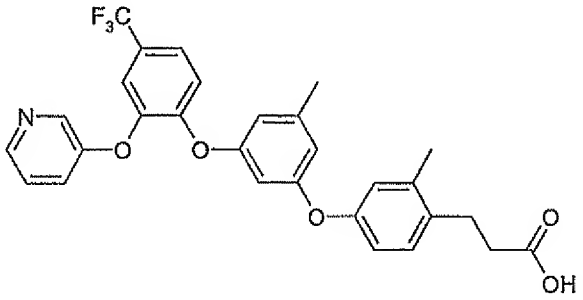


The title compound is prepared by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with 2-hydroxypyridine as in Example 45 to afford 0.010 g (8%). ^{1}H NMR

(400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{24}NO_5F_3$ 523, found 524 (M+1, 100%).

Example 48

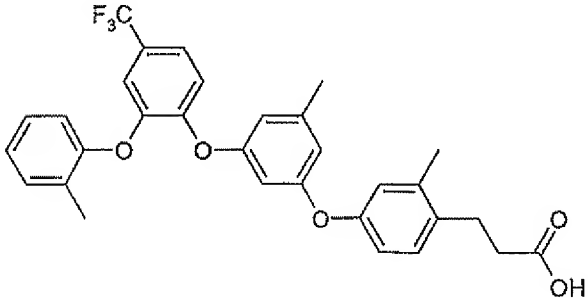
3-(2-Methyl-4-{3-methyl-5-[2-(pyridin-3-yloxy)-4-trifluoromethyl-phenoxy]-phenoxy}-phenyl)-propionic acid



The title compound is prepared by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with 3-hydroxypyridine as in Example 45 to afford 0.044 g (31%). ^1H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{29}H_{24}NO_5F_3$ 524.1685, found 524.1680.

Example 49

3-{2-Methyl-4-[3-methyl-5-(2-o-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with *o*-cresol as in Example 45 to afford 0.038 g (25%). ^1H NMR (400 MHz,